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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/613,228	07/03/2003	Arthur M. Krieg	C1037.70045US00	4680

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EXAMINER	
MINNIFIELD, NITA M	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 10/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/613,228	KRIEG, ARTHUR M.	
	Examiner	Art Unit	
	N. M. Minnifield	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,8-12,14,16-20,22,27-32,43 and 99* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *See Continuation Sheet* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892) 2pps.
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-5,8-20,22,27-32,43,45-57,63-65,70-73,76-80,83,84,88,89,94,95,97 and 99.
Continuation of Disposition of Claims: Claims withdrawn from consideration are 5,15,13,45-57,63-65,70-73,76-80,83,84,88,89,94,95 and 97.

Continuation of Disposition of Claims: Claims subject to restriction and/or election requirement are 5,13,15,45-57,63-65,70-73,76-80,83,84,88,89,94,95 and 97.

DETAILED ACTION

Response to Amendment

1. Applicant's amendment filed July 27, 2005 is acknowledged and has been entered. Claims 6, 7, 21, 23-26, 33-42, 44, 58-62, 66-69, 74, 75, 81, 82, 85-87, 90-93, 96 and 98 have been canceled. Claims 16-20, 22, 27-32 and 43 have been amended. New claim 99 has been added. Claims 1-4, 8-12, 14, 16-20, 27-32, 43 and 99 are pending in the instant application. All rejections have been withdrawn in view of Applicant's amendment to the claims and/or comments, with the exception of those discussed below.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. This application contains claims 5, 13, 15, 45-57, 63-65, 70-7, 76-80, 83, 84, 88, 89, 94, 95 and 97 are drawn to an invention and/or species nonelected with traverse in paper filed December 27, 2004. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

4. Claims 1-4, 8-11, 16-20, 22, 29-32, 43 and 99 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 41-46, 52-56 and 58-60 of copending Application No. 10/816,220. Although the conflicting claims are not identical, they are not patentably distinct from each other because they both claim a composition

comprising a immunostimulatory nucleic acid molecule, Applicant's SEQ ID NO: 1 is SEQ ID NO: 152 set forth in claim 56 of Application 10/816,220. Both applications set forth claims directed to the composition also comprising an antigen, which can be a cancer antigen as well as additional adjuvants and modes of administration.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

This provisional rejection is maintained for the reasons of record. Applicant's arguments filed July 27, 2005 have been fully considered but they are not persuasive. Applicant has stated that "[W]ithout conceding the Examiner's position, Applicant defers substantive rebuttal until the cited application is allowed. This provisional rejection is maintained until a properly filed terminal disclaimer has been received or the claims have been amended sufficient to obviate this provisional rejection.

5. Claims 1-4, 8-12, 14, 16-20, 22, 29-32, 43 and 99 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a composition comprising (or consisting of) SEQ ID NO: 1. The composition also comprises cancer antigen, adjuvants as well as anti-cancer agents. Based on the components of the composition it would appear that the intended use of the claimed composition is for *in vivo* use in a method to

treat cancer in a subject. However, none of the examples set forth in the specification disclose the use of the claimed composition, that being a SEQ ID NO: 1 and a cancer antigen with any of the other possible components (cytokines, adjuvants, mucosal adjuvants and anti-cancer agents, etc) for treatment of a cancer in a subject.

The specification discloses the use of SEQ ID NO: 1 (ODN 10106) in *in vitro* assays that indicate that the nucleic acid can activate TLR9, human B cells and B cell proliferation, all *in vitro*. Th1 dominated immune responses were observed and IFN-alpha secretion. The only *in vivo* evidence provided in the specification is found on page 95, where mice were immunized with ODN 10106 and HBsAg, an immune response was achieved. There is no evidence of *in vivo* use of the claimed composition comprising SEQ ID NO: 1, cancer antigen, with any of the other additional components. The specification does not predict or teach any positive therapeutic benefit (i.e. treating or preventing cancer or immune response) correlated with the administration of the claimed composition in a rodent or non-rodent subject.

The state of the art with regard to cancer is unpredictable. Tumor cells *in vivo* simply do not display their unique antigens in ways that are easily recognized by cytotoxic T lymphocytes (Ezzell; see also Forni et al). Tumors are classified as immunogenic or non-immunogenic, solid or hematological in nature. Effective cancer strategies should be designed to deal effectively with the nature of each of these classifications. Further, it has been an art-recognized experience that for any novel therapy, the transition from the laboratory to the clinic (animal experiments to bedside) is a quantum leap (Chatterjee et al.). Results obtained under controlled conditions and in inbred animals often differ from the clinical response obtained in

patients. This applies in particular to strategies based on immune responses. McCluskie et al teaches that T-rich immunostimulatory nucleic acids do not induce an immune response. *In vitro* animal model studies have not correlated well with *in vivo* clinical trial results in patients. Since the therapeutic indices of immunotherapeutic regimens can be species- and model-dependent, it is not clear that reliance in the *in vitro* stimulation of immune cells with the claimed immunostimulatory nucleic acid and the *in vivo* mouse and non-human primate experimental models with CpG containing ODNs accurately reflects the relative efficacy of the claimed therapeutic strategy based upon *in vitro* stimulation as disclosed in the specification.

There is insufficient evidence that would lead a person of skill in the art to predict that the claimed composition would have the ability to treat or prevent cancer or to induce an immune response in a subject. The specification provides insufficient guidance to practice the claimed invention. In view of the lack of the predictability of the art to which the invention pertains and the lack of established clinical protocols for effective adjuvant therapies, undue experimentation would be required to practice the claimed invention with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed invention.

This rejection is maintained for the reasons of record. Applicant's arguments filed July 27, 2005 have been fully considered but they are not persuasive. Applicant has asserted that the claims define a specific nucleotide sequence (SEQ ID NO: 1 and that the claimed composition may further comprise other elements such as antigens, adjuvants, and other disease-specific agents. The claimed

compositions can be used to stimulate immune responses but they are not limited to any particular in vitro or in vivo use. Thus they can be used therapeutically or non-therapeutically. However, Applicant elected one antigen species, a cancer antigen and one specific therapeutic agent, an anti-cancer agent. The claims are examined for enablement of how to use the claimed invention with regard to a composition comprising the nucleotide sequence (SEQ ID NO: 1) and a cancer antigen, or anti-cancer agent. The specification has not shown that the claimed composition can be used therapeutically or non-therapeutically. The specification has not taught how to use the claimed invention. It is also noted that the state of the art indicates CpG containing oligonucleotides are currently being investigated for exerting their immunotherapeutic effects in various organisms. Biological responses to the administration of CpG containing oligonucleotides vary, however, depending on the mode of administration and the organism (see McCluskie et al Molecular Med., 1999, 5/5:287-300 in its entirety, and especially on p. 296; see Krieg et al, Immunology Today, 2000, 21/10:521-526, especially p. 524). Wohlleben et al 2001 (TRENDS in Immunology, 2001, 22/11:618-626) teaches that it has been reported that the application of CpG-ODNs can cause septic shock in mice. A further potential problem might be the development of autoimmune disease after application of CpG-DNA. Residual autoreactive T cells might become sufficiently activated to cause disease after encountering APCs that have been unspecifically activated by CpG-DNA (p. 620, col. 2) Wohlleben et al teaches that all approaches that induce Th1 responses have the potential side effects of Th1-cell-mediated inflammation, potentially causing serious tissue damage (p. 624, col. 1). Weiner (J. Leukocytes Biology, 2000, 68:456-463) states furthermore that the molecular mechanisms of CpG oligonucleotides'

immunostimulatory effects are not yet understood (see p. 461). And while the biological effects of some chemical modifications have been studied for CpG containing oligonucleotides, such as 2'-O-methyl modifications, phosphorothioate internucleotide linkages and 5-methyl cytosine substitutions, the incorporation and positioning of chemical modifications relative to the CpG dinucleotide are highly unpredictable (see Agrawal et al Molecular Med. Today, 2000, 6:72-81, especially on pp. 78-80; pages 31-32 of the instant specification).

Applicant has asserted that at the time of filing the state of the art was aware of immunostimulatory nucleic acids, including CpG immunostimulatory nucleic acids. Applicant has asserted that several patents were issued before the effective filing date of the instant application that disclose the ability of the immuno-stimulatory nucleic acids to stimulate innate and antigen-specific immune responses. Therefore Applicant asserts that the art was familiar with how to make the nucleic acids and how to use such nucleic acids to stimulate immune responses in vitro or in vivo. With regard to the level of predictability in the art, Applicant has also asserted that treatment of cancer is not a limitation of the claimed invention and the Examiner has put forth an enablement standard in excess of what the law requires. Applicant has provided numerous references (Appendix A) to indicate the therapeutic utility of CpG in the treatment of cancers. Applicant has also asserted that the references cited by the Examiner are not directed to immunostimulatory nucleic acid based therapy.

With regard to these arguments, it is noted that the Examiner has never questioned that the specification and the state of the art know how to make the nucleic acids, but whether the claimed composition can be used. The question of enablement is whether one can make and use the claimed invention. It is clear that

the claimed invention can be made. However, the specification does not set forth any enablement for the composition being used in treatment of cancer; which is the use contemplated in the specification. It is noted that the specification contemplates that the composition comprising CpG, a cancer antigen, and anti-cancer agents (i.e. cancer vaccine, chemotherapeutic agent, immunotherapeutic agent) is to be used in the treatment of cancers (see for example: p. 3, l. 12-19; p. 4, l. 20-30; p. 5, l. 11-18; p. 6, 13-15; p. 6, l. 16-30) The Examiner acknowledges the issued patents, but the information and evidence of enablement for the issued patents are not of record in this application and further, the scope of the claims in the issued patents is different than the pending claims. Further, the state of the art with regard to cancer therapy is unpredictable, in addition CpG immunostimulatory nucleic acid molecules in cancer therapy is unpredictable. Donnelly et al (Nature Medicine, 2003, 9/11:1354-1356) teaches that over many decades various approaches to eliciting both innate and acquired immune responses against tumors have been tried, some with a degree of success. However, immunotherapy has yet to be incorporated into first-line therapies for more than a very few types of cancers such as the use of IL-2 immunotherapy for metastatic renal cell carcinoma (p. 1354, col. 2). Further, Donnelly teaches that treating cancer with something that looks more like a modern-day vaccine, with a defined antigen and an optimized adjuvant and delivery platform, is still in the future (see p. 1354, col. 2; see also col. 3). "A variety of anti-tumor vaccine clinical trials have been undertaken. In spite of the large number of these trials, and the plethora of distinct approaches investigated, there has been little evidence of clinical efficacy. Furthermore, precise correlates of clinical effects and immunological responses have been lacking." (DeGruijl et al, Nature Medicine, 1999, 5/10:1124-1125, see p.

1124, col. 1) Bitton R. J. (Current Opinion in Molecular Therapeutics, 2004, 6/1:17-25) teaches that developing cancer vaccines to treat solid tumors is not an easy task (abstract). Bitton teaches that "immune editing", in part, explains why many cancer vaccines work in animal models but not in a clinical setting (abstract). Bitton describes the various cancer vaccine strategies and evaluates the evidence supporting their efficacy (abstract). Bitton indicates that the final picture with regard to cancer vaccines is confusing and comparison of different vaccine strategies is almost impossible because of the different strategies from different groups. Further, most of the vaccines are still experimental, far from being approved by regulatory authorities and their clinical utility is almost negligible (abstract). Bitton teaches that therapeutic vaccines have proved to have little use in cancer treatment and that in fact in almost every well-designed, well-controlled, randomized phase III trial, they have failed to demonstrate any significant improvement in overall or disease-free survival (p. 17, col. 2; Table 2). "It is clear that most vaccines are indeed effective immunogens, but they do not seem to be effective at triggering anticancer responses. Tumor size reduction, the classic endpoint in clinical development of cytotoxic drugs does not seem to be useful in evaluating cancer vaccines; tumor stabilization might be more valuable. Finally, there is no evidence of improvement in overall survival or disease-free survival. The implementation of well-designed randomized phase III trials is urgently required." (pp. 24-25)

With regard to CpG in the treatment of cancers, Weiner (J. Leukocyte Biology, 2000, 68:455-463) indicates that there is therapeutic potential in cancer treatment for CpG as an immune adjuvant (Table 1) and that there are a number of scenarios where CpG could be used as a component of cancer immunotherapy,

each of these areas is under intensive investigation (p. 458, col. 1). Studies in a tumor model (38C13 murine lymphoma) indicate that CpG was just as effective as CFA at inducing an antigen-specific antibody response (p. 458, col. 2). Weiner teaches that "[P]reliminary studies suggest CpG ODN can be effective in a variety of scenarios when used alone or in combination with other agents. Despite this promise we still do not understand the molecular mechanisms responsible for the immunostimulatory effects of CpG ODN. All CpG ODN are not alike, and more needs to be learned about the heterogeneous responses that occur based on host organism, cell subset, or CpG ODN sequence. Most importantly, we have not yet explored their clinical effects. Further work with CpG ODN in both the laboratory and the clinic is needed before we can know their true promise as investigational immunological and therapeutic agents." (p. 461, col. 1) Krieg et al (Pharmacology and Therapeutics, 1999, 84:113-120) teaches that CpG has NK-stimulating properties and suggest that it can be used in immunotherapy of tumors, yet Krieg et al also indicates that many or even most types of tumors are relatively resistant to NK-mediated lysis (p. 117, col. 2). Ballas et al (J. Immunology, 2001, 167:4878-4886) teaches that the selection of optimal CpG ODN for cancer immunotherapy depends upon a careful analysis of the cellular specificities of various CpG motifs and an understanding of the cellular mechanisms responsible for the antitumor activity in a particular tumor (abstract). Ballas et al teaches that a single CpG ODN cannot be used to treat all cancers and tumors. Although several CpG ODN were active as sole immunotherapeutic agents in two tumor models, different motifs were optimal in each model. CpG ODN 1585 was optimal against B16 melanoma and its effects were dependent on NK cells. CpG ODN 1826 was optimal in a lymphoma model and its effects appeared to require NK (early) and T

cells (late). These results illustrate that the potent distinct CpG motifs can be custom-tailored for each desired immune effect (p. 4878, col. 2; see also p. 4885, col. 1; see also Wooldridge et al, Current Opinion Oncology, 2003, 15:440-445). Agrawal et al (TRENDS in Molecular Medicine, 2002, 8/3:114-120) also teaches that different effects are observed with different CpG ODNs.

In view of the fact that there are so many different cancer vaccines, immunotherapies and chemotherapeutic agents being used or developed for the treatment of the myriad of cancers and tumors; and the fact that CpG ODN has only been shown to useful in one or two tumor animal models, but does not show the same type of results in clinical trials, it would require undue experimentation for a skilled artisan to practice the claimed invention. The state of the art is unpredictable with regard to both cancer therapies and the use and number of different CpG ODN. Applicant's specification does not set forth any enablement using SEQ ID NO: 1 in a composition (alone or with a cancer antigen) in a cancer treatment or cancer immunotherapy. The art teaches that there are no established clinical protocols for effective cancer therapies. There would be undue experimentation required to practice the claimed invention with a reasonable expectation of success of the claimed composition being successful in cancer treatment or cancer therapies, absent a specific and detailed description in applicant's specification of how to effectively use the claimed compositions and absent working examples providing evidence which is reasonably predictive of the use of the claimed composition for use in cancer therapies for the myriad of known cancers and/or tumors.

Applicant has asserted that a claimed composition is not limited by a recited use and if any enabled use would reasonably correlate with the entire scope of that

claim is sufficient to preclude a rejection for enablement based on how to use. However, the specification has not enabled claimed SEQ ID NO: 1 and cancer antigen in a composition that is useful to treat any and all cancers as is the scope of the claims. The claims are read in light of the specification and the intended use in the specification of a composition comprising SEQ ID NO: 1 and a cancer antigen and an anti-cancer agent, or cancer vaccine is to treat cancer in a subject. Further, with regard to the numerous references and press releases in Appendix A, it is not clear that CPG 7909 is actually the claimed SEQ ID NO: 1. The evidence of enablement must be commensurate in scope with the claimed invention.

6. No claims are allowed.

7. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

8. The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record in the parent related applications.

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 571-272-0860. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette R.F. Smith can be reached on 571-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

N. M. Minnifield
Primary Examiner
Art Unit 1645

NMM
October 5, 2005